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Form Approved Through OMB No. 0

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

GRANT APPLICATION

Follow instructions carefully. Type in the unshaded areas only. Type density must be 10 c.p.i.

LEAVE BLANK FOR PHS USE ONLY.		
Type	Activity	Number
Review Group		Formerly
Council/Board (Month, Year)		Date Received

1. TITLE OF PROJECT (Do not exceed 56 typewriter spaces.)
Cardiotoxicity of Streptococcal Pyrogenic Exotoxins

2a. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT ☒ NO ☐ YES (If "YES," state number and t
Number: Title:

2b. TYPE OF GRANT PROGRAM

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

3a. NAME (Last, first, middle)
Schlievert, Patrick M.

3b. DEGREE(S)
Ph.D.

3c. SOCIAL SECURITY NO.
485-56-9034

3d. POSITION TITLE
Professor

3e. MAILING ADDRESS (Street, city, state, zip code)
Department of Microbiology
University of Minnesota
Box 196 UMHC
420 Delaware Street, SE
Minneapolis, MN 55455-0312

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Microbiology

3g. MAJOR SUBDIVISION
Medical School

3h. TELEPHONE AND FAX (Area code, number and extension)
TEL: 612-624-1484
FAX: 612-626-0623

BITNET/INTERNET ADDRESS micro@lenti.med.umn.edu

4. HUMAN SUBJECTS — If "Yes," exemption no. or IRB approval date — 4b. Assurance of compliance no.
☒ 4a. NO ☐ YES

5. VERTEBRATE ANIMALS — If "Yes," IACUC approval date — 5b. Animal welf assurance
☐ 5a. NO ☒ YES A3456

6. DATES OF ENTIRE PROPOSED PROJECT PERIOD		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR ENTIRE PROPOSED PROJECT PERIOD	
From (MM/DD/YY)	Through (MM/DD/YY)	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs
		89,687	125,562	279,967	391,954

9. PERFORMANCE SITES (Organizations and addresses)
960 Mayo Building
University of Minnesota
420 Delaware Street SE
Minneapolis, MN 55455

10. INVENTIONS AND PATENTS (Competing continuation application only)
☒ NO ☐ YES — If "YES," ☐ Previously reported ☐ Not previously reported

11. NAME OF APPLICANT ORGANIZATION
University of Minnesota
ADDRESS
Research Technology Transfer Admi
1100 Washington Avenue S, Ste. 201
Minneapolis, MN 55415-1226

12. TYPE OF ORGANIZATION
☒ Public: Specify ☐ Federal ☒ State ☐ Local
☐ Private Nonprofit
☐ Forprofit (General) ☐ Forprofit (Small Business)

13. ENTITY IDENTIFICATION NUMBER
1-416007513-A8

Congressional District
3

14. BIOMEDICAL RESEARCH SUPPORT GRANT CREDIT
Code: 01 Identification: School of Medicine

15. NAME OF ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
A.R. Potami
TELEPHONE 612-624-1648
FAX 612-624-4843
TITLE Associate Vice President
ADDRESS ORTTA
1100 Washington Avenue S, Ste 201
Minneapolis, MN 55415-1226

BITNET/INTERNET ADDRESS arpotami@ortta.umn.edu

16. NAME OF OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
A.R. Potami or Mary Lou Weiss
TELEPHONE 612-624-5856
FAX 612-624-4843
TITLE Assistant Director
ADDRESS ORTTA
1100 Washington Avenue S., Ste. 201
Minneapolis, MN 55415-1226

BITNET/INTERNET ADDRESS mweiss@ortta.umn.edu

17. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application. Willful provision of false information is a criminal offense (U.S. Code, Title 18, Section 1001). I am aware that any false, fictitious, or fraudulent statements may, in addition to other remedies available to the Government, subject me to civil penalties under the Program Fraud Civil Remedies Act of 1986 (45 CFR 79).

SIGNATURE OF PERSON NAMED IN 3a. (In ink. "Per" signature not acceptable.)
Patrick Schlievert

DATE

18. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense (U.S. Code, Title 18, Section 1001). I am aware that any false, fictitious, or fraudulent statement may, in addition to other remedies available to the Government, subject me to civil penalties under the Program Fraud Civil Remedies Act of 1986 (45 CFR 79).

SIGNATURE OF PERSON NAMED IN 16. (In ink. "Per" signature not acceptable.)

DATE

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. DO NOT EXCEED THE SPACE PROVIDED.

The long term goals of this project are two-fold: (a) to evaluate the role of streptococcal pyrogenic exotoxins (SPEs, scarlet fever toxins) in causing both acute TSS-like illnesses and delayed sequelae such as acute rheumatic fever, guttate psoriasis, and vascular diseases, and (b) to analyze the structure-function relationships among the SPEs and between the SPEs and staphylococcal enterotoxins and TSST-1. It is hoped that the latter studies will ultimately clarify the molecular mechanism of action of the toxins.

Experiments will be done to prepare sufficient SPEs A and C for crystallization and three-dimensional structure determination. Toxin purification will be accomplished by ethanol precipitation from large cultures, toxin resolubilization in pH 4.0 acetate-buffered saline, and preparative thin layer isoelectric focusing. Crystallization and three dimensional structure determination will be done in collaboration with Douglas H. Ohlendorf, Department of Biochemistry, University of Minnesota. Domains and amino acids on SPE types A and C required for biological activity (pyrogenicity, enhancement of lethal endotoxin shock, enhancement of cardiotoxicity, ability to induce TSS when administered subcutaneously in miniosmotic pumps, and superantigenicity) and lipopolysaccharide binding will be localized through use of PCR mutagenesis, both site specific and through deletion of entire domains. Nucleotide sequencing will be done to verify changed amino acids and structure determination will be done to assess alteration of 3-dimensional structure of mutants. Although not an objective, it is anticipated these latter studies will also localize domains recognized by monoclonal antibodies to the two SPEs.

PERSONNEL ENGAGED ON PROJECT, INCLUDING CONSULTANTS/COLLABORATORS. *Use continuation pages as needed* to provide the required information in the format shown below on *all* individuals participating in the scientific execution of the project.

Name Patrick M. Schlievert	Degree(s) Ph.D.	Social Security No. 485-56-9034
Position Title Professor	Date of Birth (MM/DD/YY) 06/02/49	Role on Project PI
Organization University of Minnesota		Department Microbiology
Name Douglas H. Ohlendorf	Degree(s) Ph.D.	Social Security No. 328-44-8583
Position Title Associate Professor	Date of Birth (MM/DD/YY) 09/19/50	Role on Project Collaborator
Organization University of Minnesota		Department Biochemistry
Name	Degree(s)	Social Security No.
Position Title	Date of Birth (MM/DD/YY)	Role on Project
Organization		Department
Name	Degree(s)	Social Security No.
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